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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,355	07/05/2006	Karin Butz	085449-0180	6994

22428 7590 11/27/2006

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/553,355	BUTZ ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-43* is/are pending in the application.

4a) Of the above claim(s) *28-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-27 and 37-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-5-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Sequence Rule Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

CFR §1.821(d) reads as follows:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims or the patent application.

Figure 1a as well as pages 21-23 of the instant application contain nucleic acid sequences which are not preceded by "SEQ ID NO:". Applicants are reminded that either the brief description of drawings for the Figure 1a or Figure itself should make a reference to the sequences by use of the sequence identifiers in accordance with CFR §1.821 through 1.825. Applicants are also reminded that the nucleic acid sequences disclosed in Figure 1a and pages 21-23 of the specification must be entered in the paper copy of sequence listing as well as CRF. See Notice to Comply. Any response to this action must correct this deficiency, as this requirement will not be held in abeyance.

Response to Arguments/Election/Restriction

Applicant's election with traverse of SEQ ID NO:2 in the reply filed on October 30, 2006 is acknowledged. The traversal is on the ground(s) that there is no serious burden on the examiner to search all 8 distinct SEQ ID NOs. This is not found persuasive because the instant application is filed under 35 U.S.C. 371 and 37 CFR 1.495, which therefore is subject to the "unity of invention" rule. See 37 CFR §1.475 or 35 U.S.C. 121 and 372, for example. Further, the issue of "search burden" is neither stated nor asserted in the Office action mailed to the applicant on September 29, 2006. Since the instant application is not a U.S. filed application, the rules stated in MPEP §803 regarding search burden does not apply, thus applicant's argument is irrelevant and moot.

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 20-43 are pending and claims 28-36 and SEQ ID NOs:1, 3, 4, 6, 7, 8, and 9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Accordingly, claims 20-27 and 37-43 reading on the elected SEQ ID NO:2 are currently under examination on the merits.

Specification

The disclosure is objected to because of the following informalities: pages 21-23 of the specification and Figure 1a contain sequences that do not comply with sequence rules. See Notice to Comply. Appropriate correction is required.

Claim Objections

Claims 22 and 26 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 20 and 24 claim "administering said siRNA to said therapy-resistant tumor cells" in lines 4-5, and claims 22 and 26 claim "The method of claim 20 (and claim 24, respectively), wherein the siRNA is delivered into a therapy-resistant tumor cell". The only apparent difference between claims 20, 24 and claims 22, 26 is the wording: "administering" compared to "delivered into", which are synonymous in meaning in plain English. Hence, claims 22 and 26, as claimed, do not further limit the subject matter claimed in claims 20 and 24, respectively. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

In light of the above, claims 22 and 26 are also objected to under 37 CFR 1.75 as being substantial duplicates of claims 20 and 24. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 20, 24, 37-38 and 43 are objected to for containing non-elected subject matter. Appropriate correction is required.

Claim 24 is objected to because of the following informalities: It appears that a hyphen is omitted between "therapy" and "resistant" in line 1. Appropriate correction is required.

Claim 43 is objected to because of the following informalities: It appears that a comma is omitted between "9" and "a pharmaceutically" in line 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-22 and 41-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 recites the limitation "said therapy-resistant tumor cells" in lines 4-5. There is insufficient antecedent basis for this limitation in the claim because the recitation of "therapy-resistant tumor cells" in lines 4-5 is the first occurrence.

Furthermore, claim 20 and claim 24 recite "preparing siRNA from a nucleic acid" in line 1 and 2, respectively. It is unclear and vague what is encompassed by the claim language "preparing" because "preparing" can mean a number of different subject matter such as synthesizing, modifying, and obtaining, for example. Further, the term "preparing" also reads on

an apparatus or a machine that produces the claimed invention, siRNA. Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. That is, one skilled in the art cannot recognize the metes and bounds set forth by the term "preparing", thus rendering claims 20 and 24 as well as their dependent claims indefinite.

In light of the fact that the term "preparing" can be construed to mean an apparatus to make a product, claim 20 claims both an apparatus and a method of using the apparatus because the claim recites "and administering said siRNA to said therapy-resistant tumor cells" (lines 4-5). A single claim which claims both an apparatus and the method steps of using the apparatus is indefinite under 35 U.S.C. 112, second paragraph. In Ex parte Lyell, 17 USPQ2d 1548 (Bd. Pat. App. & Inter. 1990). See also MPEP §2173.05(p).

Claims 21-22 recite the limitation "The method of claim 20" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 20 does not recite the word "method".

Claim 41 recites the limitation "The method of claim 38, wherein the therapy-resistant tumor is selected from" in 1. There is insufficient antecedent basis for this limitation in the claim because claim 38 recites "therapy-resistant tumors" in a plural form.

Claim 42 recites the limitation "The method of claim 38, wherein the therapy-resistant tumor is cervical carcinoma" in lines 1-2. There is insufficient antecedent basis for this

limitation in the claim because claim 38 does not recite "cervical carcinoma" and because claim 38 recites "therapy-resistant tumors" in a plural form.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-27 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of sensitizing therapy-resistant tumor cells and a method for down-regulating Livin comprising preparing an siRNA and administering SEQ ID NO:4 *in vitro* using liposomes, does not reasonably provide enablement for a method of sensitizing therapy-resistant tumor cells comprising preparing an siRNA and administering SEQ ID NO:2 or a fragment thereof *in vivo* using liposomes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient

evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of claims 20-27 and 37 encompasses both *in vivo* and *in vitro* methods; however, the instant specification exemplifies only *in vitro* methods in Examples 1-6 without providing any specific guidance regarding *in vivo* applications of the instantly claimed invention. The examples provided in the specification are specific for an siRNA molecule comprising SEQ ID NO:4, which is a hairpin siRNA molecule containing SEQ ID NO:2. This exemplified molecule is identified as pSUPER-Livin-2 and the specification demonstrates that pSUPER-Livin-2 exerts inhibitory effects on the expression level of Livin in HeLa cervical carcinoma cells and MeWo melanoma cells. Nevertheless, the specification does not describe any inhibitory effects of pSUPER-Livin-2 *in vivo,* nor does it show working examples wherein other siRNA molecules besides the exemplified pSUPER-Livin-2 are able to inhibit the Livin expression either *in vitro* or *in vivo*.

Problems related to *in vivo* use of nucleic acids, especially double-stranded RNA duplex remain unresolved in the art even after the instant application was filed. See for example Lu et al. (*Advances in Genetics,* 2005, 54:117-142) and Sioud (*Methods in Molecular Biology,* 2005, 309:237-249). Such problems include the inability to specifically deliver an effective concentration of an siRNA molecule to a target cell, such that a target gene is inhibited to a

degree necessary to result in an effective, long-lasting inhibition of gene expression commensurate with a pharmacological or therapeutic effect.

For instance, Lu et al. state the complicity and unpredictability of siRNA-mediated inhibition in a specific target tissue/cell of animal systems as below:

> "However, *in vivo* delivery of siRNA into specific tissues of animal disease is much more complicated. Although increasing numbers of studies on target identification and validation using siRNA *in vitro* have been reported, limited reports of *in vivo* studies have indicated a lack of effective delivery methods for siRNA agents. The key to *in vivo* application is a delivery system that transports the siRNA into the target tissue and into the cell cytoplasm..." (page 122)

Further, Sioud states the transient effect as well as complex nature of siRNA/liposome-mediated gene inhibition as below:

> "Despite some encouraging results, however, the liposomes still have not the characteristics to be perfect carriers because of toxicity, short circulation time, and limited intracellular delivery for target cells... As mentioned earlier, one of the drawbacks of synthetic siRNAs is the transient nature of the inhibition in mammalian cells." (page 238)

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant sensitization of therapy-resistant tumor cells, as claimed. The specification provides *in vitro* transfection of Livin siRNA molecules into cell lines; however, cell culture examples are generally not predictive of *in vivo* results and the methods of delivery of the exemplified cell lines would not be applicable to those for *in vivo* applications. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Given these teachings, the skilled artisan would not know *a priori* whether introduction of siRNAs *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the siRNAs reaching the proper cell in a sufficient concentration and

remaining for a sufficient time to provide successful inhibition of expression of the Livin gene *in vivo*.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using siRNAs in *in vivo* applications in any organism. The teachings of the siRNA-mediated gene therapy art does not provide that guidance, such that the skilled artisan would be able to practice the claimed methods in an *in vivo* setting.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for a method of sensitizing therapy-resistant tumor cells *in vivo* by introducing siRNA molecules into an organism. In view of the foregoing, the amount of experimentation required is such that one of skill in the art cannot practice the invention commensurate in scope with the claims without undue experimentation and therefore, claims 20-27 and 37 are enabled only as far as the *in vitro* method of making and administering, sensitizing therapy-resistant tumor cells, and reducing Livin expression comprising SEQ ID NO:2.

Claims 38-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for treatment or a medicament for the treatment of therapy-resistant tumors comprising an siRNA containing SEQ ID NO:2.

Since the claims are directed to a method/medicament for treating therapy-resistant tumors comprising an siRNA molecule, the claims are considered to encompass only *in vivo* therapeutic use.

As stated above for claims 20-27 and 37, the *in vivo* application of siRNA molecules for therapeutic purpose is neither predictable nor routine in the art as taught by Lu et al. (*supra*), for example. Further, the instant specification provides no guidance with regard to how to use the method of treatment since it provides only the *in vitro* transfection data. In light of the enablement issues stated above on pages 7-10 herein, it is concluded that one of ordinary skill in the art cannot practice the instantly claimed invention without undue experimentation in view of the totality of the factors listed above on pages 7-8 herein.

In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), the Court ruled that a rejection under 35 U.S.C. 112, first paragraph for lack of enablement was appropriate given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims.

Accordingly, in view of the totality of the factors/reasons stated above, it would require undue experimentation for one skilled in the art to practice the entire scope of the claimed invention at the time of filing, absent evidence to the contrary.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 20 is rejected under 35 U.S.C. 101 because it claims both an apparatus "preparing siRNA" and a method of using the product made by the apparatus "administering said siRNA to said therapy-resistant tumor cells". MPEP §2173.05(p) states that a single claim which claims both an apparatus and the method steps of using the apparatus may also be rejected under 35 U.S.C. 101 based on the theory that the claim is directed to neither a "process" nor a "machine," but rather embraces or overlaps two different statutory classes of invention set forth in 35 U.S.C. 101 which is drafted so as to set forth the statutory classes of invention in the alternative only.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 20-27 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Khvorova et al. (US 2005/0245475 A1, earliest effective filing date is November 14, 2002), as evidenced by Bennett et al. (US 2004/0005565 A1).

The claims are drawn to a method of administering an siRNA molecule comprising SEQ ID NO:2 to therapy-resistant tumor cells, wherein the siRNA is most preferably 19 nucleotides in

length and is administered by using liposome and wherein the method results in down-regulation of livin and sensitization of therapy-resistant tumor cells.

The instant specification defines the phrase "fragment and derivative" as "nucleic acids that may differ from the original nucleic acid in that they are extended or shortened on either the 5' or the 3' end, on both ends or internally, or extended on one end, and shortened on the other end" and those that have "one or more nucleotides or the original sequence are substituted by other nucleotides and/or (chemically) modified" under the condition that the nucleotides have the function of the resulting siRNA. See page 3. Given the broadest reasonable interpretation of the phrase "fragment or derivative thereof" consistent with the instant specification, the instantly claimed SEQ ID NO:2, a fragment or derivative thereof will be construed to read on any nucleic acids comprising any portion of the SEQ ID NO:2, which exhibits an siRNA function.

Khvorova et al. teach an siRNA molecule of SEQ ID NO:1220975 (19-mer), of which nucleotides 1-15 align perfectly with the instant nucleotides of 5-19 of SEQ ID NO:2. They teach a method of transfecting an siRNA molecule of their invention into cultured cell lines *in vitro* via liposomes (paragraphs 0110, 0319, and 0322-0323). They teach that siRNA mediates gene silencing and thus inhibits gene expression (paragraphs 0004-0009). They teach that their siRNA molecules can be used for silencing a broad range of genes, particularly those that are associated with cancer (paragraph 0251).

Bennett et al. teach that Livin is expressed in a number of tumor cell lines, particularly in melanoma cell lines which display resistance to drug-induced apoptosis (paragraph 0007).

In light of the teachings of Bennett et al., it is clear that one of Livin's inherent biological properties is its high expression profile in therapy-resistant melanoma cells. Hence, the method

of Khvorova et al. comprising administering SEQ ID NO:1220975 into cultured cancer cells via liposome would inherently result in a sensitization of therapy-resistant cancer cells and inhibition of Livin expression *in vitro* in therapy-resistant cancer cells, as evidenced by the teachings of Bennett et al. Accordingly, the instantly claimed invention taken as a whole is clearly taught by Khvorova et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-27 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. (US 2004/0005565 A1) in view of Fire et al. (US 6,506,559 B1).

Bennett et al. teach SEQ ID NO:50 (20-mer), of which nucleotides 7-20 are perfectly complementary to the nucleotides 6-19 of the instant SEQ ID NO:2. They teach an antisense oligonucleotide comprising SEQ ID NO:50 is targeted to a nucleic acid encoding Livin and that it specifically hybridizes with and inhibits the expression of the Livin gene. They teach that the Livin antisense oligonucleotide comprising SEQ ID NO:50 is useful for preparing a composition for treating hyper-proliferative disorder or aberrant apoptosis. See Example 15. They teach that the Livin antisense molecule can be delivered into cells via liposomes (paragraph 0094). They also teach that Livin is expressed in a number of tumor cell lines, particularly in melanoma cell lines which display resistance to drug-induced apoptosis (paragraph 0007). They describe that the fact that Livin is involved in regulation of apoptosis indicates that Livin can be a therapeutic target for disorders arising from aberrant apoptosis (paragraph 0008). Bennett et al. do not teach an siRNA molecule targeted to Livin.

Fire et al. teach that short interfering double-stranded RNA (siRNA) molecules mediate sequence-specific inhibition of gene expression, which is known as RNA interference (RNAi) phenomenon (columns 3-6 and column 14, lines 52-53). They further teach that the siRNA-mediated inhibition (RNAi) is at least 100-fold more effective than an equivalent antisense approach (column 3, lines 25-32). They teach that siRNA molecules can be used to inhibit gene expression in cancer cells of any type (column 10, lines 26-27).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the Livin antisense oligonucleotide of Bennett et al. with the siRNA molecule of Fire et al. One of ordinary skill in the art would have been motivated to make such modification with a reasonable expectation of success because Bennett et al. has already taught

the structure as well as nucleic acid sequence of the Livin antisense oligonucleotide (identified as SEQ ID NO:50) at the time of filing, and because Fire et al. expressly teach that an siRNA molecule is a more potent inhibitor of gene expression than an antisense oligonucleotide. The skilled artisan would have been motivated to administer the siRNA molecule of Fire et al. to therapy-resistant cancer cells because Bennett et al. teach that Livin is particularly highly expressed in therapy(drug)-resistant cancer cells and that Livin is implicated in regulation of apoptosis. Thus, the skilled artisan would have been motivated to decrease the Livin expression in therapy-resistant cells by administering a Livin siRNA molecule so as to regulate aberrant apoptotic cells, thereby sensitizing the therapy-resistant cells, as claimed in the instant case. Since the siRNA technology of gene inhibition, the target sequence for the Livin gene, the fact that Livin is highly expressed in cancer cells that are resistant to drug-induced apoptosis, and the involvement of Livin in regulation of cell apoptosis were all known in the art at the time of filing, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time the invention was made.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

TC 1600

JANE ZARA, PH.D.
PRIMARY EXAMINER

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 37 CFR §1.821(g). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. §§1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. §§1.821-1.825. Applicants attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a Sequence Listing as required by 37 C.F.R. §1.821(c).
- [ ] 3. A copy of the Sequence Listing in computer readable form has not been submitted as required by 37 C.F.R. §1.821(e).
- [ ] 4. A copy of the Sequence Listing in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. §1.822 and/or 1.823, as indicated on the attached copy of the marked-up Raw Sequence Listing.
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. §1.825(d).
- [ ] 6. The paper copy of the Sequence Listing is not the same as the computer readable from of the Sequence Listing as required by 37 C.F.R. §1.821(e).
- [ ] 7. Other:

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the Sequence Listing. (If the unidentified sequences are not provided on the CRF)
- [X] An initial or substitute paper copy of the Sequence Listing, as well as an amendment directing its entry into the specification. (If the unidentified sequences are not provided in the paper copy)
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). (If a new paper and/or CRF are required)

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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